201-14490

May 21, 2003

By Mail
Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program – Test Plan Submission from HERTG
Registration Number

Dear Administrator Whitman:

The American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG) submits for review and public comment its test plan report, as well as related robust summaries, for the single chemical, "Formaldehyde, Reaction Product with Tetrapropenyl Phenol, Methylamine and Sulfur" (CAS # 68855-34-5) under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program. The HERTG understands that there will be a 120-day review period for the test plan report and that all comments generated by or provided to EPA will be forwarded to the HERTG for consideration.

Thank you in advance for your attention to this matter. If you have any questions regarding the test plan report or the robust summaries, or HERTG's activities associated with the Challenge Program, please contact Sarah McLallen at 703-741-5607 (telephone), 703-74 l-609 1 (telefax) or Sarah-McLallen@americanchemistry.com (e-mail).

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

cc: HERTG members

201-14490A

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

TEST PLAN

For

Formaldehyde, Reaction Product with Tetrapropenyl Phenol, Methylamine and Sulfur

Prepared by
The American Chemistry Council
Petroleum Additives Panel
Health, Environmental, and Regulatory Task Group

May 2003

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LIST OF MEMBER COMPANIES IN THE HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

B.P. plc

Chevron Oronite Company, LLC

Crompton Corporation

Ethyl Corporation

ExxonMobil Chemical Company

Ferro Corporation

Infineum

The Lubrizol Corporation

Rhein Chemie Corporation

Rhodia, Inc.

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1.0 INTRODUCTION

In March 1999, the American Chemistry Council (formerly the Chemical Manufacturers Association) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to address data needs for certain chemicals listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program. This test plan follows up on that commitment. Specifically, this test plan sets forth how the HERTG intends to address testing information for the following substance:

- Formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur (CAS No.: 68855-34-5)

This document sets out the findings of the data review process, and sets forth a proposed test plan to satisfy parts of the required test battery for endpoints without data that would be considered adequate under the program.

EPA guidance on the HPV Challenge Program indicates that the primary purpose of the program is to encourage "the chemical industry . . . to voluntarily compile a Screening Information Data Set (SIDS) on all chemicals on the US HPV list." (EPA, "Development of Chemical Categories in the HPV Challenge Program," p. 1. In preparing this test plan the following steps were undertaken:

> Step 1: A search was conducted for relevant published and unpublished literature on formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.
>
> Step 2: The compiled data was evaluated for adequacy in accordance with EPA guidance.

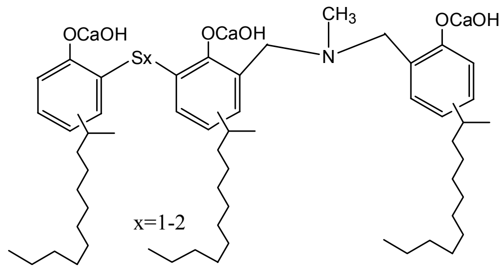
This test plan, including the following data assessment with the proposed testing scheme for the petroleum additive formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur, will be made available to EPA and to the public for review.

2.0 GENERAL SUBSTANCE INFORMATION

The substance that is the subject of this test plan is used as petroleum additives in petroleum base stocks. The chemical names, CAS Registry Numbers, molecular weight, chemical structure for this substance are presented below.

> Chemical Name: Formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.
>
> Chemical Abstract Service Registry Number: 68855-34-5
>
> Molecular Weight: 967-1179 gm/mol

Chemical Structure:



3.0 EXPOSURE AND USE INFORMATION

<u>Manufacture</u>

This substance is a sulfurized calcium long chain alkyl phenol mannich phenate. It is prepared by a mannich reaction with tetrapropenyl phenol (CAS No. 74499-35-7, C10-C15 alkyl phenol), methyl amine, and formaldehyde. The intermediate Mannich alkyl phenol is then neutralized with calcium hydroxide in the presence of a highly sulfurized alkyl phenol (CAS 122384-85-4) to give the end product, Formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur. These reactions occur in a solvent composed of highly refined lubricant base oil. Thus the "active ingredient" is never isolated during the life cycle of this substance. This is done for two reasons: 1) the kinetics of the chemical reactions used in the manufacturing process are optimized when highly refined lubricating base oils are used as the reaction solvent, and 2) lubricant additives diluted in highly refined lubricating base oils are required to control viscosities during blending with other additives or with additional highly refined lubricating base oil to make finished lubricants. To meet the required viscosity for this substance, the concentration of highly refined lubricating base oil is typically 35 wt%.

<u>Use</u>

This substance is used to formulate finished lubricating oils used in railroad diesel engines. It is used as a high temperature detergent to reduce deposits on pistons and engine crankcases. This substance is generally sold to finished oil blenders in additive packages, where the concentration ranges from 5 to 20 wt.%. These additive packages are then blended into finished oils where the typical concentration of this substance ranges from 1 to 3 wt.% in the finished oil.

<u>Distribution</u>

This substance is manufactured and blended into additive packages at plants owned by members of the HERTG. Finished lubricants are blended at facilities owned by our customers. Additive packages are shipped to customers in bulk in ships, isocontainers, railroad tank cars, tank trucks or in 55-gallon steel drums. The bulk additive packages are stored in bulk storage tanks at the customer blending sites. Finished oils are blended by pumping the lubricating oil blend stocks and the additive package from their storage tanks through computer controlled valves that meter the precise delivery of the components into a blending tank. After blending, the finished lubricant products are sold in bulk and shipped in tank trucks to large industrial users, such as manufacturing facilities and facilities that service railroad engine fleets. Finished lubricants are also packaged into 55-gallon drums, 5-gallon pails, and one-gallon and one-quart containers for sale to smaller industrial users. Sales to non-industrial users do not occur.

Based on these uses, the potentially exposed populations include (1) workers involved in the manufacture of this substance, blending it into additive packages, and blending the additive packages into finished lubricants; (2) quality assurance workers who sample and analyze this substance to ensure that it meets specifications; (3) workers involved in the transfer and transport of this substance and additive packages or finished lubricants that contain it; and (4) mechanics who may come into contact with both fresh and used lubricants while working on engines. The most likely route of exposure for these substances is skin and eye contact. Manufacturing, quality assurance, and transportation workers will likely have access to engineering controls and wear protective clothing to eliminate exposure. Mechanics wear protective clothing, but often work without gloves or eye protection. The most likely source of environmental exposure is accidental spills at manufacturing sites and during transport.

4.0 PHYSICAL CHEMICAL PROPERTIES

Physical Description
Formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur is a dark amber liquid with a petroleum odor at ambient temperature.

Molecular Weight
The molecular weight of this substance ranges from 967 to 1167 daltons depending on the nature of the sulfur cross-bridge (monosulfur or disulfur) and the carbon chain distribution in propylenetetramer (C10-C15).

Specific Gravity
The specific gravity of this substance as manufactured in highly refined lubricating base oil is 0.989 @ 60^{o}F.

Viscosity
The viscosity of this substance as manufactured in highly refined lubricating base oil is 4,960 cSt @ 40^{o}C.

Melting Point
This substance as manufactured in highly refined lubricating base oil is a liquid at ambient temperature.

Boiling Point
The use of this substance in finished lubricants requires that they be thermally and chemically stable under high temperatures (>100^{o}C). Typically, the highly refined lubricating base oil in this substance boils at temperatures above 300^{o}C. The boiling point of the theoretical "de-oiled" substance will be determined by modeling.

Vapor Pressure
A solid material is produced when one attempts to "de-oil" this substance. Thus, the vapor pressure of this substance as manufactured in highly refined lubricating base oil can be estimated from the vapor pressure of the base oil. Typically, highly refined lubricating base oils have a low vapor pressure, < 10^{-10} Pa @ 25^{o}C.

Water solubility
The water solubility of this substance as manufactured in highly refined lubricating base oil will be determined experimentally.

Partition Coefficient
The partition coefficient of this substance in oil and water will be determined by modeling.

The boiling point and partition coefficient (Kow) for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur will be determined using computer modeling as discussed in the EPA document titled "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program." The model proposed for this purpose is the EPIWIN, version 3.02[1], which was developed by the Syracuse Research Corporation.

5.0 Environmental Fate Data

5.1. Physicochemical Properties Relevant to Environmental Fate

The environmental fate of a substance is dependent on how that substance partitions among environmental compartments (i.e., air, soil, sediment, suspended sediment, water, and biota). The physicochemical properties of a substance influence the way in which a substance will degrade. The important environmental degradation pathways are biodegradation, hydrolysis, and photodegradation. Biodegradation is a measure of the potential of compounds to be degraded by microorganisms. Hydrolysis is a reaction in which a water molecule or hydroxide ion substitutes for another atom or group of atoms present in an organic molecule. Photodegradation is the degradation of a chemical compound as a result of absorption of solar radiation.

[1] Environmental Science Center- Syracuse Research Corporation- EPI for windows.

The physicochemical properties of the parent substance and its degradation by products will also influence the way in which this substance will partition among environmental compartments. Substances characterized by a low vapor pressure do not partition into air to any great extent. Similarly, substances that are characterized by low water solubility do not partition extensively into water. Substances that do not partition into air and water to any great extent tend to partition into soil and sediments.

5.2 Biodegradability

5.2.1 Test Methodologies

Chemical biodegradation involves a series of microbially-mediated reactions that may require many kinds of microorganisms acting together to degrade the parent substance. Primary degradation (i.e., loss of parent chemical) can be determined analytically by measuring dissolved organic carbon (DOC) for water-soluble chemicals, infrared absorbance, or by a chemical-specific detection method. Ultimate degradation (also called mineralization, i.e., complete utilization of the substance to produce carbon dioxide, water, mineral salts, and microbial biomass) can be determined by measuring oxygen consumption or carbon dioxide evolution relative to the theoretical levels that can be achieved based on an elemental analysis of the chemical under investigation.

5.2.2 Summary of Available Data

The HERTG could not locate published or unpublished biogegradation studies of formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.

5.2.3 Data Assessment and Test Plan for Biodegradability

Biodegradation testing, according to OECD Test Guideline 301, will be conducted.

5.3 Hydrolysis

5.3.1 Test Methodologies

The potential for a substance to hydrolyze in water is assessed as a function of pH (OECD Guideline 111, *Hydrolysis as a Function of pH*[2]). When an organic molecule undergoes hydrolysis, a nucleophile (water or hydroxide ion) attacks an electrophile and displaces a leaving group (e.g., halogen, phenoxide).[3] Potentially hydrolyzable groups include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters[4]. The lack of a suitable leaving group renders compounds resistant to hydrolysis.

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[2] Organization for Economic Cooperation and Development (OECD) (1993) OECD Guidelines for Testing of Chemicals. OECD. Paris, France.
[3] W. Lyman et al. (1990) *Handbook of Chemical Estimation Methods*. Chapter 8.
[4] W.J. Lyman, W.F. Reehl, and D.H. Rosenblatt. (1982) Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co. New York, NY, USA.

5.3.2 Summary of Available Data

The HERTG could not locate published or unpublished hydrolysis studies of formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.

5.3.3 Data Assessment and Test Plan for Hydrolysis

Hydrolysis testing, according to OECD Test Guideline 111, will be conducted.

5.4 Photodegradation

5.4.1 Test Methodologies

A prerequisite of photodegradation is the ability of one or more bonds of a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer.

The Atmospheric Oxidation Potential (AOP) of a substance can be characterized using the modeling program AOPWIN. This computer simulation is recommended in the Agency's recently released structure activity review (SAR) guidance for HPV chemicals.

5.4.2 Summary of Available Data

The HERTG could not locate published or unpublished photodegradation studies for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.

5.4.3 Data Assessment and Test Plan for Photodegradation

The Atmospheric Oxidation Potential (AOP) of this substance will be characterized using the modeling program AOPWIN.

5.5 Fugacity Modeling

5.5.1 Modeling Methodologies

Fugacity-based multimedia fate modeling compares the relative distribution of chemicals among environmental compartments. A widely used model for this approach is the EQC model[5].

There are multiple levels of the EQC model. In the document, "Determining the Adequacy of Existing Data", EPA states that it accepts Level I fugacity modeling to estimate transport/distribution values. The Agency states that Level III model data are considered "more realistic and useful for estimating a chemical's fate in the environment on a regional basis". The EQC Level I model utilizes input of basic chemical properties, including molecular weight, vapor pressure, and water solubility to calculate percent distribution within a standardized environment. EQC Level III uses

[5] Equilibrium Criterion Model- Environmental Modeling Centre as developed by D. Mackay.

these parameters to evaluate chemical distribution based on discharge rates into air, water, and soil, as well as degradation rates in air, water, soil, and sediment.

5.5.2 Summary of Available Data
The HERTG could not locate published or unpublished fugacity-based multimedia fate modeling data for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.

5.5.3 Test Plan for Fugacity
The relative distribution of formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur among environmental compartments will be evaluated using Level I Fugacity modeling.

Input data to run the EQC Level I model will require an additional computer model to estimate physical/chemical properties from a structure. The model used for this purpose will be EPIWIN, version 3.02[6], which was developed by the Syracuse Research Corporation. EPIWIN includes algorithms for estimating all physical and chemical properties needed for the EQC model.

6.0 ECOTOXICOLOGY DATA

6.1 Aquatic Ecotoxicity Testing

6.1.2 Test Methodologies
Acute aquatic ecotoxicity tests are usually conducted with three species that represent three trophic levels in the aquatic environment: fish, invertebrates, and algae. The fish acute toxicity test (OECD Guideline 203, *Fish, Acute Toxicity Test*) establishes the lethality of a substance to a fish during a 96-hour exposure period. The acute invertebrate test (OECD Guideline 202, *Daphnia sp., Acute Immobilization Test and Reproduction Test*) establishes the lethality of a substance to an invertebrate, typically a daphnid (*Daphnia magna*), during a 48-hour exposure period. The alga growth inhibition test (OECD Guideline 201, *Alga, Growth Inhibition Test*) establishes the potential of a substance to inhibit alga growth, typically using the freshwater unicellular green algae, *Pseudokirchneriella subcapitata* (formerly called *Selenastrum capricornutum*), during a 96-hour exposure period.

In *flow-through tests*, organisms are continually exposed to fresh chemical concentrations in each treatment level in the incoming water and there is greater assurance than with other test methods that the exposure levels and water quality remains constant throughout the test. Although flow-through testing is the preferred method, it is only applicable for chemicals that have adequate water solubility for testing.

[6] Environmental Science Center- Syracuse Research Corporation- EPI for windows.

In *static tests*, organisms are exposed in still water that is not renewed. The chemical is added to the dilution water to produce the desired test concentrations. Test organisms are then placed in the test chambers, and there is no change of water at any time during the test. There is less assurance that the test concentrations test organisms are exposed to will remain constant because test material can be adsorbed onto test chambers, degraded, volatilized, or otherwise changed during the test. Nevertheless, due to limitations of other test systems for non-volatile materials, the static test has been widely used, especially for testing organisms such as algae and *Daphnia*.

The *static-renewal test* is similar to a static test because it is conducted in still water, but the test solutions and control water are renewed periodically, usually every 24 hours. Daily test solution renewal provides a greater likelihood that the exposure concentrations will remain stable throughout the test. Daily renewals cannot be done in the algae test, and usually not in *Daphnia* tests, because the process of separation and replenishment would cause a discontinuity in the alga growth rate and it can stress, coat, or entrap *Daphnia* in any surface film during renewals. OECD considers the use of static test for fish, *Daphnia*, algae and the use of static renewal test for fish to be appropriate for testing poorly soluble chemicals provided that test solution preparation uses water accommodated fraction or water soluble fraction methods.[7]

6.2. Aquatic Toxicity of Formaldehyde, Reaction Product with Tetrapropenyl Phenol, Methylamine and Sulfur

In general, the toxicity of a substance to an organism is limited by mechanisms of uptake and movement to target organs. Characteristics such as smaller molecular size and a lesser degree of ionization increase the ability of a substance to passively cross biological membranes. However, the soluble fraction of a compound in water represents the chemical fraction responsible for toxicity to aquatic organisms. Therefore, aquatic toxicity can be limited by the water solubility of a substance.

The water solubility of this substance will be determined as described above. If the water solubility of this substance is low as predicted by its physical chemical properties, the acute aquatic toxicity should be low due to limited bioavailability to aquatic organisms.

[7] Organization for Economic Cooperation and Development (OECD) (2000). Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures. OECD Environmental Health and Safety Publications, Series on Testing and Assessment No.23, Paris, France.

6.2.1 Summary of Available Data

The HERTG could not locate published or unpublished acute aquatic ecotoxicity data for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.

6.2.2 Data Assessment and Test Plan for Acute Aquatic Ecotoxicity

Acute aquatic ecotoxicity testing in fish, invertebrates, and algae will be conducted according to OECD Test Guidelines 201, 202 and 203 after the water solubility of this substance is determined.

7.0 MAMMALIAN TOXICOLOGY DATA

7.1 Acute Mammalian Toxicity

7.1.1 Acute Toxicity Test Methodology

Acute toxicity studies investigate the effect(s) of a single exposure to a relatively high dose of a substance. Potential routes of exposure for acute toxicity assays include oral, dermal, and inhalation. Oral toxicity assays are conducted by administering test material to fasted animals (typically rats or mice) in a single gavage dose. Acute dermal toxicity tests are conducted by administering test material to the shaved skin on the back of the test animal (typically rats or rabbits) and allowing the test material to stay in contact with the skin application site for a specific duration (usually 24 hours). Historically, lethality is a primary end-point of concern in acute toxicity studies, and the traditional index of oral and dermal potency is the median lethal dose that causes mortality in 50 percent of the test animals (LD_{50}).. In addition to lethality, acute toxicity studies also provide insights regarding potential systemic toxicity through careful observation and recording of clinical signs and symptoms of toxicity as well as through detailed examination of tissues and organ systems.

7.1.2 Summary of Available Data

Acute oral and dermal toxicity studies are available for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur. In both studies, the LD_{50}s are greater than 5 g/kg indicating a low concern for toxicity.

7.1.3 Data Assessment and Test Plan for Acute Mammalian Toxicity

Adequate acute oral and dermal toxicity tests were performed for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur prior to the development of the OECD Test Guidelines. These studies are considered appropriate for inclusion in this test plan. Additional acute mammalian toxicity testing will not be conducted.

7.2 Mutagenicity

7.2.1 Mutagenicity Test Methodology

Genetic toxicology is concerned with the effects of substances on genetic material (i.e., DNA and chromosomes). Within genetic material, the gene is the simplest functional unit composed of DNA. Mutations are generally non-lethal, heritable changes to genes, which may arise spontaneously or as a consequence of xenobiotic exposure. Genetic mutations are commonly measured in bacterial and mammalian cells. The simplest test systems measure the occurrence of a base-pair substitution mutation in which a single nucleotide is changed followed by a subsequent change in the complementary nucleotide on the other DNA strand. Frame shift mutations occur following the deletion or insertion of one or more nucleotides, which then changes the "reading frame" for the remainder of the gene or multiple genes. Genetic testing for these types of point mutations is generally accomplished by *in vitro* cellular assays for forward or reverse mutations. A forward mutation occurs when there is a detectable change in native DNA whereas a reverse mutation occurs when a mutated cell is returned to its initial phenotype. Both base-pair substitutions and frame shift mutations are routinely measured in bacterial cells by measuring the ability of a cell to acquire the capability to grow in an environment missing an essential amino acid. In these tests, a large number of cells are examined to demonstrate a significant increase in the frequencies of mutations that occur over the frequency of spontaneous mutations.

Chromosomal aberrations are large scale numerical or structural alterations in eukaryotic chromosomes including deletions (visualized as breaks), translocations (exchanges), non-disjunction (aneuploidy), and mitotic recombination. Chromosomal breakage is the classical end point in chromosomal aberration assays. Substances that induce structural changes in chromosomes, especially chromosome breaks, are referred to as "clastogens." To visualize chromosomes and chromosomal aberrations following *in vitro* or *in vivo* treatment with a substance, cells are arrested in metaphase, treated to swell the chromosomes, fixed, transferred to slides and stained. The first metaphase following treatment is the time at which the greatest number of cells with damaged chromosomes may be observed. The most frequently used test systems investigate changes in mammalian cells (such as Chinese hamster ovary or lung cells; human or rat lymphocytes; or human, rat or mouse bone marrow cells) following either *in vitro* or *in vivo* exposure to the test substance. The micronucleus test is a common *in vivo* assay that measures the frequency of micronuclei formation (i.e., chromosomal fragments) in polychromatic erythrocytes.

7.2.2 Summary of Mutagenicity Data

The HERTG could not locate published or unpublished mutagenicity data for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.

7.2.3 Data Assessment and Test Plan for Mutagenicity Toxicity
Gene mutation and chromosomal aberration testing will be conducted according to OECD Test Guidelines 471 and 473.

7.3 Repeated-dose, Reproductive and Developmental Toxicity

7.3.1 Repeated-dose Toxicity Test Methodology

Repeated-dose toxicity studies evaluate the systemic effects of repeated exposure to a chemical over a significant period of the life span of an animal (rats, rabbits, or mice). Chronic repeated-dose toxicity studies are concerned with potential adverse effects upon exposure over the greater part of an organism's life span (e.g., one to two years in rodents). Subchronic repeated-dose studies are also concerned with effects caused by exposure for an extended period, but not one that constitutes a significant portion of the expected life span. Subchronic studies are useful in identifying target organ(s), and they can be used in selecting dose levels for longer-term studies. Typically, the exposure regimen in a subchronic study involves daily exposure (at least 5 consecutive days per week) for a period of at least 28 days or up to 90 days (i.e., 4 to 13 weeks). A recovery period of two to four weeks (generally included in most study designs) following completion of the dosing or exposure period provides information on whether or not the effects seen during the exposure period are reversible upon cessation of treatment. The NOAEL (no observed adverse effect level), usually expressed in mg/kg/day, defines the dose of test material that produced no significant toxicological effects. If the test material produce toxicity at the lowest dose tested (i.e., there is no defined NOAEL), the lowest dose that produced an adverse effect is defined as the LOAEL (lowest observed adverse effect level). While these studies are designed to assess systemic toxicity, the study protocol can be modified to incorporate evaluation of potential adverse reproductive and/or developmental effects.

Reproductive and developmental toxicity studies generate information on the effects of a test substance on male and female reproductive performance such as gonadal function, mating behavior, conception, and development of the conceptus, parturition, and post-partum development of the offspring. Various study designs exist, but they all involve exposure to both male and female test animals before mating. The rat is most often selected as the test species. The test substance is administered to males and females continuously at several graduated doses for at least two weeks prior to mating and until the animals are sacrificed. The males are treated for at least two more weeks. Male gonadal histopathology is carefully assessed at the end of the study. The females are treated through parturition and early lactation. The adult females and offspring are typically studied until termination on post-natal day 21, or sometimes earlier. In addition to providing data on fertility and reproduction, this study design provides information on potential developmental toxicity following prenatal and limited post-natal exposure to the test substance. An NOAEL or LOAEL is also used to describe the results of these tests, with the exception that these values are derived from effects specific to reproduction or development.

The “toxicity to reproduction” requirement in the HPV Challenge Program can be met by conducting the *Reproduction/Developmental Toxicity Screening Test* (OECD Guideline 421) or by adding this screening test to a repeated-dose study (OECD Guideline 422, *Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test*). The *One-Generation Reproduction Toxicity Study* (OECD Guideline 415) is a more comprehensive protocol for the study of the effect of a test material on reproduction and development that also meets the OECD SIDS and the HPV Challenge Program requirements.

7.3.2 Summary of Repeated-Dose Toxicity Data

The HERTG could not locate published or unpublished repeat dose, reproductive or developmental toxicity tests for formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur.

7.3.3 Data Assessment and Test Plan for Repeated-dose Toxicity

Testing is proposed in the form of OECD Test Guideline 422: A Combined Repeated Dose Toxicity Study with a Reproduction/Developmental Toxicity Screening Test.

Figure 1. SUMMARY TABLE OF AVAILABLE DATA AND PROPOSED TESTING

CAS No.: 68855-34-5	Study Results	Testing Proposed
Physical/Chemical Characteristics		
Melting Point	Not Applicable	No
Boiling Point	No Data Found	Yes
Vapor Pressure	0.0001 torr @ 20 ^{O}C	No
Water Solubility	No Data Found	Yes
Partition Coefficient	No Data Found	Yes
Environmental Fate		
Biodegradation	No Data Found	Yes
Stability in Water	No Data Found	Yes
Photodegradation	No Data Found	Yes
Fugacity	No Data Found	Yes
Ecotoxicity		
Acute Toxicity to Fish	No Data Found	Yes
Acute Toxicity to Invertebrates	No Data Found	Yes
Acute Toxicity to Algae	No Data Found	Yes
Mammalian Toxicity		
Acute Toxicity	Oral LD50 > 5 g/kg (rat) Dermal LD50 > 5 g/kg (rabbit)	No
Gene Mutation	No Data Found	Yes
Chromosomal Aberration	No Data Found	Yes
Repeated Dose Toxicity	No Data Found	Yes
Developmental Toxicity	No Data Found	Yes
Reproductive Toxicity	No Data Found	Yes

201-14490B

ROBUST SUMMARY
HEALTH ELEMENTS
ACUTE TOXICITY

Substance Group: Group 12

Summary prepared by: Petroleum Additives Panel
Health & Environmental Research Task Group

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ROBUST SUMMARY
HEALTH ELEMENTS
ACUTE TOXICITY

Test Substance	
CAS #	CAS# 68855-34-5
Chemical Name	Formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to Test Guideline 402
Test Type	Acute dermal toxicity (Limit Test)
GLP (Y/N)	N
Year (Study Performed)	1971
Species/Strain	Rabbits/New Zealand White
Sex	Male
No. of animals/group	6
Vehicle	None
Route of administration	Dermal
Dose level	0 and 5 g/kg
Dose volume	Not provided.
Control group included	Yes
Remarks field for test conditions	This study was conducted prior to the development of Test Guideline 402. This study deviated from Guideline 402 in that the skin of 3 treated animals was abraded prior to dosing. In addition the guideline calls for the evaluation of males and females using at least one dose level. This study was conducted using males only. These deviations were not considered sufficient to change the outcome of the study. Approximately 24 hours prior to topical application of the test material, the hair of each animal was closely clipped. On the day of dosing the skin of three treated animals was abraded prior to test material administration. A single dose of 5 g/kg of the undiluted test material was administered dermally to six male animals. The test material was kept in contact with the skin for a period of 24 consecutive hours under an elastic sheet. The application site was wiped clean of residual test material at the end of the 24-hour exposure period. The animals were observed for 14 days after treatment. The surviving animals were euthanized at the conclusion of the observation period. Gross necropsies were performed on all animals on Day 14.
Results	LD50 > 5.0 g/kg (males)
Remarks	No signs of toxicity were observed during the 14-day observation period. Moderate skin irritation was observed when the rabbits were unwrapped after the 24-hour exposure. At necropsy, the skin appeared to be healing and no macroscopic pathological changes were

	attributable to the test material. Pale kidneys were observed in both test and control animals.
Conclusions	The test article, when administered dermally as received to 6 male New Zealand white rabbits had an acute dermal LD50 of greater than 5.0 g/kg.
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the fact that this is a summary report.
References	Unpublished confidential business information
Other	Updated: 10/18/01

ROBUST SUMMARY
HEALTH ELEMENTS
ACUTE TOXICITY

Test Substance	
CAS #	CAS# 68855-34-5
Chemical Name	Formaldehyde, reaction product with tetrapropenyl phenol, methylamine and sulfur
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	FHSA 16CFR1500.3
Test Type	Acute oral toxicity
GLP (Y/N)	N
Year (Study Performed)	1971
Species/Strain	Rats/ Sprague-Dawley strain
Sex	Male
No. of animals/dose	10
Vehicle	None
Route of administration	Oral (intragastric)
Dose level	0 and 5.0 g/kg
Dose volume	Not provided
Control group included	Yes
Remarks field for test conditions	A single dose of the undiluted test material was administered intragastrically to ten fasted male rats. A control group was included. The animals were observed for signs of toxicity or behavioral changes daily. All animals were euthanized at the conclusion of the observation period. Gross autopsies were performed on all animals after 14 days.
Results	LD50 > 5 g/kg (males)
Remarks	No signs of toxicity were observed during the 14-day observation period. At necropsy treated and control animals exhibited pulmonary congestion and consolidation.
Conclusions	The test article, when administered as received to male Sprague-Dawley rats, had an acute oral LD50 > 5 g/kg.
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the fact that this is a summary report.
References	Unpublished confidential business information
Other	Updated: 10/18/01